Application Type	Efficacy Supplement
STN	125347.231
CBER Received Date	16 March 2015
PDUFA Goal Date	14 January 2016
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name(s)	Ralph LeBlanc,M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Jeff Roberts ,M.D., Branch Chief CRB1
	Lucia Lee, M.D. , Team Leader, CRB1
Applicant	Glaxo Smith Kline Biologicals
Established Name	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)
(Proposed) Trade Name	HIBERIX
Pharmacologic Class	vaccine
Formulation(s), including Adjuvants, etc	Solution for injection supplied as a vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent. A single dose, after reconstitution, is 0.5 ml and contains 10 mcg of purified capsular polysaccharide conjugated to approximately 25 mcg of tetanus toxoid.
Dosage Form(s) and Route(s) of Administration	Solution for intramuscular injection
Dosing Regimen	• Proposed: One dose each at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age. • Current: One booster dose at 15 months through 4 years of age (prior to fifth birthday).
Indication(s) and Intended Population(s)	Active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
BLA	biologics license application
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CSR	complete study report
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
(b) (4)	
ENERGIX-B®	Hepatitis B vaccine, recombinant [GSK]
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GSK	GlaxoSmithKline Biologicals, Inc.
HIB	Haemophilus influenza type b
HIBERIX®	Haemophilus influenza type b conjugated to tetanus toxoid [GSK]
ISE	integrated summary of efficacy
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PEDIARIX®	DTPa-IPV-HepB [GSK]
PENTACEL®	DTPa-IPV-HIB [SP]
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PK	pharmacokinetics
PMC	post marketing commitment
PMR	post marketing requirement
PREA	Pediatric Research Equity Act
PREVNAR13®	Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein] [Wyeth Pharmaceuticals Inc.]
PRP	polyribosyl-ribitol-phosphate
PRP-T	polyribosyl-ribitol-phosphate-tetanus conjugate
PRP-OMP	polyribosyl-ribitol-phosphate-outer membrane protein conjugate
PVP	pharmacovigilance plan
REMS	risk evaluation and mitigation strategy
ROTARIX®	Rotavirus vaccine, live, oral [GSK]
RMS/BLA	regulatory management system for the biologics license application
SAE	serious adverse event
SP	Sanofi Pasteur, Inc.

1. Executive Summary

Hiberix is a vaccine that contains capsular polysaccharide from *Hemophilus influenzae* type b (Hib) conjugated to tetanus toxoid. Hiberix is currently approved as a booster dose at 15 months through 4 years of age for the prevention of invasive Hib disease. The safety and immunogenicity data from a single study, study HIB-097, was submitted in this supplement to the Hiberix Biologics License Application (BLA) to support the use of Hiberix as a primary immunization series in children 6 weeks to 14 months of age. The primary series is administered at 2, 4 and 6 months of age. The first dose may be given as early as 6 weeks of age.

Hiberix was approved in August 2009 under the Accelerated Approval (AA) regulations (21 CFR 601.41) to address the shortage of Hib vaccine in the U.S. at the time. Study HIB-097 was designed to generate the safety and immunogenicity data necessary to: (1) verify and describe the clinical benefit of Hiberix in 15 month to 4 year olds to satisfy AA requirements; and (2) provide data to support the approval of Hiberix as a primary series in children 6 weeks to 14 months of age in accordance with the requirements of the Pediatric Research Equity Act (PREA) (21 U.S.C., 355c). Only the data related to the primary immunization series in infants were reviewed under this supplement. By agreement with CBER, safety and immunogenicity data in children 15 months and older will be submitted as a separate BLA supplement (sBLA). Separate sBLAs were needed since the data required under the AA regulations would not support extension of the indication to children less than 15 months of age, which would be outside the age indication under accelerated approval.

Study HIB-097 was a phase 3, randomized, multicenter study. The treatment assignment was blinded in the following manner: double-blind for the immunogenicity and lot consistency evaluation of 3 lots of Hiberix, single blind and controlled for the evaluation of the safety and immunogenicity of Hiberix compared to a US licensed monovalent Hib vaccine, ActHIB (Sanofi Pasteur, Inc.), and open label for comparisons of Hiberix to DTPa-IPV/Hib vaccine (Pentacel; Sanofi Pasteur, Inc.). For each study group, the Hib vaccine was co-administered with vaccines (at separate injection sites) recommended by the ACIP for routine infant immunization.

Study HIB-097 was conducted at 67 sites in the U.S. A total of 4,003 subjects were randomized to five study groups with a ratio of 2:2:2:1:1 (Hiberix Lots A, B, and C, AcHIB, Pentacel). With regard to concomitantly administered vaccines, for groups that received Hiberix Lots A, B and C, subjects received 3 doses of Hiberix by lot, co-administered with 3 doses of Pediarix (GSK Biologicals, Inc.) and Prevnar13 (Wyeth Pharmaceuticals, Inc.), and 2 doses of Rotarix (GSK Biological, Inc.); the two control Groups (ActHIB group, Pentacel group) received

3 doses of ActHIB co-administered with 3 doses of Pediarix and Prevnar13 and 2 doses of Rotarix or 3 doses of Pentacel co-administered with 3 doses of Prevnar13*,* 3 doses of Engerix-B (GSK Biologicals, Inc.) and 2 doses of Rotarix.

Statistical analyses of seven primary objectives were performed in a hierarchical manner, as follows: lot to lot consistency of three lots of Hiberix; non-inferiority of Hiberix compared to ActHIB one month after the primary series (administered at ages 2, 4 and 6 months) using anti-PRP antibody concentrations ≥ 1.0/ug/mL and ≥0.15ug/mL; and non-inferiority of immune responses to antigens contained in co-administered vaccines (diphtheria and tetanus, pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), poliovirus types 1,2 and 3, and thirteen pneumococcal serotypes*).*

Immunogenicity

Lot to lot consistency: The primary objective to demonstrate lot-to-lot consistency of 3 manufacturing lots of Hiberix was not met due to a higher anti-PRP GMC reported for Lot B [6.32] than for Lot A [4.99] and Lot C [4.42], which resulted in the 95% CI for the lower limit (LL) of the ratio between Lot A to Lot B to be 0.64 [less than the 0.67 LL criteria]. However, from a clinical perspective, the differences in lot to lot consistency are statistically significant but unlikely to be clinically significant.

Non-inferiority of Hiberix to ActHIB: The criterion for non-inferiority was met for one of the two non-inferiority primary objectives. One month after completion of the primary series (i.e. at 7 months of age)

- The lower limit of the 95% CI for the difference (Hiberix [Lots A, B and C combined] minus ActHIB) in the percentage of subjects with anti-PRP concentrations ≥1.0 ug/mL was -12.3%, which was lower than the predefined limit for non-inferiority (-10%); 81.2% and 89.8% of subjects in the Hiberix and ActHIB group, respectively, achieved anti-PRP concentrations ≥1.0 ug/mL.
- The lower limit of the 95% CI for the difference (Hiberix [pooled lots] minus ActHIB) in the percentage of subjects with anti-PRP concentrations ≥0.15 ug/mL was -1.98, which was higher than the predefined limit for non-inferiority (-5%); 96.6% and 96.7% of subjects in the Hiberix group and ActHIB group, respectively, achieved anti-PRP concentrations of ≥0.15 ug/mL.

Supportive immunogenicity data indicated that:

- By 14 months of age (prior to the booster dose) Hiberix vs. ActHib: The percentages of subjects with anti-PRP concentrations ≥ 1.0ug/mL were similar between the two groups [Hiberix, 32.2% and ActHIB 27.0%] by 14 months of age (prior to the booster dose of Hib vaccine).
- Hiberix vs. Pentacel (DTaP-IPV/Hib), post-dose #3: Analyses of anti-PRP immune responses following DTaP-IPV/Hib vaccination, another US licensed Hib-containing vaccine, showed that the percentage of subjects

with anti-PRP concentrations ≥1.0 ug/mL was numerically higher following Hiberix vaccination (81.2%; 95% CI 79.2%, 83.1%] than after Pentacel vaccination (78.3%; 95% CI 72.7%, 83.2%].
- The percentages of subjects with anti-PRP concentrations ≥0.15 ug/mL were 96.6% and 92.5% after the third Hiberix and Pentacel vaccination, respectively.

The immunogenicity data altogether support the effectiveness (inferred from an established serological marker of protection, antibodies to PRP) of Hiberix.

Non-inferiority of immune responses to co-administered vaccines:
All non-inferiority criteria were met for comparisons of immune response among the study group that received Hiberix with ACIP-recommended infant vaccines compared to corresponding responses among the study group that received the same infant vaccines with ActHIB.

Safety
In total (5 study groups), 3,552 of 4003 vaccinated subjects completed the study HIB-097 through one (1) month after the primary vaccine series. The solicited local and systemic adverse reactions following Hiberix vaccination were mainly mild and occurred at rates that were within the range observed for other pediatric vaccines. For all study groups,

- The most frequently reported solicited local adverse event was injection site pain; overall, 7-13% of all subjects experienced an AE categorized as grade 3, depending on the study group and dose administered.
- Irritability was the most frequently reported solicited general adverse event. Overall, Grade 3 fever [rectal temperature ≥39.5C] was reported for 0.4-1.4% of subjects.
- Upper Respiratory Tract Infection [URTI], cough and otitis media were the most commonly reported unsolicited general adverse events.
- The most common New Onset of Chronic Diseases [NOCDs] reported during the study were atopic dermatitis, asthma and eczema, which occurred at rates of ≤1.2% in each of the groups.

Serious Adverse Events [SAEs] were reported in 3.6% of subjects in the Hiberix group; 4.6% in the ActHIB group; and 4.0% in the Pentacel group. Five SAEs were classified as related to the investigational product by the investigator (normal sleep myoclonus, Kawasaki Disease, afebrile seizure and involuntary muscle contraction of one leg were each reported in the Hiberix group), and each of the medical conditions described above resolved by one (1) month after the third dose of vaccine. CBER review of the case narratives did not reveal any evidence for a causal relationship for the sleep myoclonus, Kawasaki Disease, and the involuntary muscle contraction and these SAEs were removed from the final version of the label. One (1) case of possible seizure in the ActHIB group was reported. No deaths were reported in the study.

Special Populations and Demographic Groups
There were no significant differences in the sex of subjects enrolled in the three Hib vaccine groups. Overall, approximately 60% of subjects were white, 9-10% were African American at 9-10%, 8% were American Indian or Alaskan Native, and 7% were Asian. Immune response parameters were reported by sex and by race as white or other. The percentage of female subjects with anti-PRP concentrations ≥1.0ug/mL were generally higher compared to males; similar trends were observed for subjects with backgrounds categorized as 'other' compared to white. In this reviewer's opinion, the magnitude of the differences by gender or race is not clinically significant. There were no notable differences in the percentages of subjects with anti-PRP concentration ≥0.15ug/mL.

PREA (Pediatric Research Equity Act) Requirements)
A partial waiver to conduct studies in infants from birth to 6 weeks and for children 5 years to <17 years of age was granted. The safety and immunogenicity data from study HIB-097 fulfilled the PREA requirement to evaluate the safety and immunogenicity of Hiberix in infants 6 weeks through 14 months of age. Therefore, all PREA requirements will be fulfilled upon approval of this supplement.

Pharmacovigilance Plan
From a clinical perspective, the applicant's plan to conduct routine pharmacovigilance in the post-marketing period, based upon reporting of SAEs, deaths and invasive *Haemophilus influenzae* type b disease in vaccinated children, is acceptable.

Based upon the data submitted in this supplement and the risk-benefit assessment, this reviewer recommends approval of this efficacy supplement.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Haemophilus influenzae type b infection, caused by this gram negative cocco-bacillus, can result in a range of specific illnesses ranging from otitis media to bacteremia, meningitis, pneumonia, septic arthritis, pericarditis and epiglottis. The Center For Disease Control MMWR of February 28, 2014, "Prevention and Control of Haemophilus influenzae Type b Disease," summarizes the impact of routine HIB vaccination in the U.S.:

"Before 1985, Haemophilus influenzae type b (Hib) was the leading cause of bacterial meningitis and a common cause of other invasive diseases (e.g., epiglottitis, pneumonia, septic arthritis, cellulitis, purulent pericarditis, and bacteremia) among U.S. children aged <5 years (1). Meningitis occurred in approximately two thirds of children with invasive Hib disease; 15%–30% of survivors had hearing impairment or severe permanent neurologic sequelae. Approximately 4% of all cases were fatal (2). The first polysaccharide Hib vaccine was introduced in the United States in 1985, followed by conjugate

Hib vaccines in 1987 and 1989. During 1989–2000, the annual incidence of invasive Hib disease in children aged <5 years decreased by 99%, to less than one case per 100,000 children (3–7). During 2000–2012, the average annual incidence rate of invasive Hib disease in children aged <5 years in the United States remained below the Healthy People 2020 goal of 0.27/100,000 (8) (data available at http://www.cdc.gov/abcs/reports-findings/surv-reports.html) (Figures 1 and 2). Studies have demonstrated that vaccination with Hib conjugate vaccine leads to decreases in oropharyngeal colonization among both vaccinated and unvaccinated children (9–11); the prevalence of Hib carriage has decreased among preschool aged children from 2%–7% in the pre-vaccine era to <1% in the vaccine era (9,12)."

Although *Haemophilus influenzae* type b disease can be treated with antibiotics, it is often a sudden onset and rapidly fulminant condition and there is substantial morbidity and mortality attributable to HIB disease even with prompt introduction of effective antibiotic therapy. The introduction of efficacious immunization to prevent invasive *Haemophilus influenzae* type b disease by a primary series of three vaccinations at 2, 4 and 6 months of age and a booster dose at 15 months of age has been a major public health achievement in reducing the burden of serious disease attributable to these bacteria.

2.3 Safety and Efficacy of Pharmacologically Related Products

Three monovalent HIB vaccines [two PRP-T vaccines and one PRP-OMP vaccine] and three combination Hib vaccines [PRP-OMP-HepB; DTaP-IPV/PRP-T; and MenCY/PRP-T] are licensed and available in the U.S.

2.4 Previous Human Experience with the Product (Including Foreign Experience): Hiberix has been licensed in the U.S. since 2009 for use as a booster dose in children15 months to 4 years of age. Hiberix has been widely used internationally in infants and toddlers (3-dose infant primary immunization series + 1 booster dose in the second year of life) for over 19 years. Please see the CBER OBE review memo for details.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

A pre-sBLA meeting was held between the applicant and the agency on March 14, 2014. The Agency advised the applicant that the data submitted in support of the primary series at 2, 4 and 6 months of age should be submitted separately from the data submitted in support of the booster dose at 15 months of age, because the data pertaining to the booster phase was not complete and the data for the primary series was ready to be submitted to CBER for review. Additionally, CBER advised that data submitted in support of a change in indication cannot be submitted along with data to fulfill an accelerated approval

PMR. Thus, two separate efficacy supplements would be submitted to fulfill the two separate post-marketing requirements (PMRs) at the time of the original Hiberix approval. Those two PMRs are:
To conduct Study Hib-097, a comparative safety and immunogenicity clinical trial of primary and booster immunization with Hiberix® relative to U.S. licensed control vaccines.[AA PMR]; and
Deferred pediatric study (Study Hib-097) under PREA for the prevention of invasive disease caused by *H. influenzae* type b in pediatric patients ages 6 weeks to 14 months. [PREA PMR].

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2.6 Other Relevant Background Information

None.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this efficacy sBLA was adequately organized and integrated to enable a complete review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

One study was submitted in support of this efficacy sBLA. That study, HIB-097, was conducted under U.S. IND 14151 and included 67 sites, all in the U.S. The study was conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form contained all the essential element of informed consent as stated in 21CFR 50.25. Institutional Review Board approval was obtained for the original protocol, and all protocol amendments.

3.3 Financial Disclosures

Covered clinical study (name and/or number):HIB-097[Study 112957]		
Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 386 U.S. investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): One [Investigator # 186738]: this investigator had a SPOOS and accounted for 1.72% of all enrollees.		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	YesX☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 285		
Is an attachment provided with the reason:	Yes X ☐	No ☐ (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see the CMC review. There were no CMC issues that impacted the conclusions of this clinical review.

4.2 Assay Validation

Please see the assay review. There were no assay issues that impacted the conclusions of this clinical review.

4.3 Nonclinical Pharmacology/Toxicology

There is no data in this submission relevant to non-clinical Pharmacology/Toxicology

4.4 Clinical Pharmacology

There is no data in this submission relevant to clinical Pharmacology.

4.4.1 Mechanism of Action

The presumed mechanism of action of this vaccine is the induction of both B and T cell immune responses directed against the major capsular polysaccharide, PRP.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

Statistical analyses of the primary objectives were performed in a hierarchical manner, as follows: lot to lot consistency of three lots of Hiberix; non-inferiority of Hiberix compared to ActHIB one month after 3 primary vaccination series (administered at ages 2, 4 and 6 months) in terms of anti-PRP antibody concentration ≥ 1.0/ug/mL and ≥0.15ug/mL; and non-inferiority of immune responses to antigens contained in co-administered vaccines (diphtheria and tetanus, pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), poliovirus types 1,2 and 3, and thirteen pneumococcal serotypes*).*

Because the first primary endpoint of lot to lot consistency was not met and the statistical analysis plan was hierarchical in nature, the statistical reviewer concluded that "Due to the hierarchical nature of the statistical testing, no further tests were to be performed or conclusions drawn for the subsequent objectives." However, the statistical reviewer stated further, "While the clinical study results did not meet the predefined statistical criteria for lot consistency and non-inferiority of Hiberix to ActHIB, the overall data generated in this study indicate that the consistency of the immune response in terms of GMCs were within observed variability of two US-licensed Hib vaccines, and non-inferiority criteria were met versus *Pentacel*, a US-licensed Hib vaccine. Furthermore, non-inferiority to *ActHIB* was observed at the 0.15 mcg/mL threshold. No immune interferences with co-administered antigens were observed, and the safety profile appears acceptable and similar to two US-licensed Hib vaccines." Please see the statistical review for further details. Finally, the statistical reviewer deferred to the clinical review to assess the clinical significance of the missed co-primary endpoints and this clinical review has determined that the relatively small statistical margin by which lot to lot consistency was missed and non-inferiority at ≥1.0 ug/ml was missed are not likely to be clinically significant.

4.6 Pharmacovigilance

The PVP submitted by the applicant is acceptable. Please refer to the PVP review by the OBE reviewer. There were no pharmacovigilance issues that impacted the conclusions of this clinical review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This s BLA was submitted electronically, and included one study, HIB-097, to support both efficacy and safety. The clinical, labeling, financial disclosure information sections of the application were reviewed, with a detailed analysis of the study report, pertinent line listings, case report forms, and datasets, and the original BLA review from 2009. Review of past and current *Haemophilus influenza* type b vaccination recommendations by the Advisory Committee on Immunization Practices also occurred in conjunction with review of current HIB U.S. surveillance data.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The major document that served as the basis for this review was the CSR for the study HIB-097. The clinical, labeling, and financial disclosure information sections of the application were reviewed, with a detailed analysis of the study report, pertinent line listings, case report forms, and datasets. Review of past and current HIB vaccination recommendations by the Advisory Committee on Immunization Practices also occurred in conjunction with review of current HIB U.S. surveillance data.

CLINICAL DATA SOURCES

All information in the following modules (m) and sections (s) were reviewed:
Amendment 0: m2 (Clinical Overview); m5 (Clinical Study Reports)
Amendment 3: m1 (s1.9.6 Responses to CBER information requests [IR] dated 29-May-2015: Pediatric assessment).
Amendment 5: m1 (s1.11.2 Responses to CBER information requests [IR] dated 5-August-2015: Narrative summaries of “international event reports” or SAE findings in table format).
Amendment 7: m1 (s1.14.1.3 Revised PI in response to CBER’s 11/9/2015 First round of labeling comments).
Amendment 8: m1 (s1.14.1.3 Revised PI in response to CBER’s 11/18/2015 (Second round) and 11/24/2015 (Third round) labeling comments).

The applicant’s written responses contained in the amendments described above were satisfactory.

5.3 Table of Studies/Clinical Trials

There was one study submitted for review as part of this sBLA submission.

Table 1. Clinical Trials for Efficacy Supplement

Study No./country/start and end date	Study description	Population	Treatment Assignment	Number of Subjects randomized
HIB-097 start date: June 18,2010 End date: August 3, 2012	A Phase III, randomized, multicenter study	6 weeks to 2 months of age at time of enrollment	Hiberix ActHIB Pentacel	2963 520 520
			Total	4003

Source: adapted from sBLA 125347.231, CSR HIB-097, table 27, p.196

5.4 Consultations

None.

5.4.1 Advisory Committee Meeting

Not applicable

5.4.2 External Consults/Collaborations

None

5.5 Literature Reviewed

The following publications are specifically cited as references in this review:

1. Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* Type b. Journal of Infectious diseases, 1984; 149:1034.

2. Peltola H, Kaythy H, Sivonen A, et al. *Haemophilus influenzae* Type b Capsular Polysaccharide Vaccine in Children: A Double-Blind Field Study of 100,000 Vaccinees 3 Months to 5 Years of Age in Finland. *Pediatrics* 1977;60:730-737.

3. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6301a1.htm

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study HIB-097

6.1.1 Objectives (Primary, Secondary, etc.)

The study had six co-primary objectives:

1. To demonstrate lot to lot consistency of three manufacturing lots of Hiberix co-administered with Pediarix, Prevnar 13 and Rotarix, following three primary vaccine doses in terms of antibody responses to PRP
2. To demonstrate non-inferiority of Hiberix to ActHIB in terms of anti-PRP antibody concentration ≥1.0ug/mL
3. To demonstrate non-inferiority of Hiberix to ActHIB in terms of anti-PRP antibody concentration ≥0.15ug/mL
4. To demonstrate non-inferiority of Pediarix co-administered with Hiberix, Prevnar 13 and Rotarix to Pediarix co-administered with ActHIB, Prevnar 13 and Rotarix, in terms of immune responses to diphtheria, tetanus, pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN] and to poliovirus types 1,2 and 3
5. To demonstrate the non-inferiority of a three dose series of Prevnar 13 co-administered with Hiberix, Rotarix and Pediarix compared to that of Prevnar 13 co-administered with ActHIB, Rotarix and Pediarix, in terms of *S. pneumonia* GMCs.
6. To rule out a 10% decrease in sero-response to PT, FHA and PRN in subjects who received Pediarix co-administered with Hiberix, Prevnar 13 and Rotarix compared to subjects who received Pediarix co-administered with ActHIB, Prevnar 13 and Rotarix, by the criteria of percentage of subjects showing an antibody concentration above a threshold that leads to 95% sero-response in the control group.

The study had seven secondary objectives:

1. To evaluate the immunogenicity of 3 manufacturing lots of *Hiberix* following 3 primary vaccine doses in terms of the percentage of subjects with anti-PRP concentrations ≥0.15 µg/mL and ≥1.0 µg/mL and in terms of anti-PRP GMCs.
2. To evaluate the immunogenicity of a 3-dose primary vaccination course of *Hiberix* co-administered with *Prevnar13, Rotarix* and *Pediarix,* that of *ActHIB,* co-administered with *Prevnar13, Rotarix* and *Pediarix* and that of *Pentacel* co-administered with *Prevnar13, Rotarix* and *Engerix-B* in terms of anti-PRP concentrations ≥0.15 µg/mL, ≥1.0 µg/mL, and in terms of anti-PRP GMCs (except for the evaluations specified in the primary objectives).
3. To evaluate the immunogenicity of a 3-dose primary vaccination course of *Pediarix* co-administered with *Hiberix, Rotarix* and *Prevnar13,* that of *Pediarix* co-administered with *ActHIB, Rotarix* and *Prevnar13* and that of *Pentacel* co-administered with *Prevnar13, Rotarix* and *Engerix-B* with respect to diphtheria, tetanus, PT, FHA, PRN, hepatitis B and poliovirus types 1, 2 and 3 (except for the evaluations specified in the primary objectives)
4. To evaluate the immunogenicity of a 3-dose primary vaccination course of *Prevnar13* co-administered with *Hiberix, Rotarix* and *Pediarix,* of *Prevnar13* co-administered with *ActHIB, Rotarix* and *Pediarix* and of *Prevnar13* co-administered with *Pentacel, Rotarix* and *Engerix-B* in terms of *S.pneumoniae* GMCs and antibody concentrations ≥ 0.05µg/mL, ≥ 0.2

µg/mL, ≥ 1.0 µg/mL (except for the evaluations specified in the primary objectives)

5. To compare the immunogenicity of *Hiberix* co-administered with *Pediarix*, *Prevnar13* and *Rotarix* to *Pentacel* co-administered with *Prevnar13, Rotarix* and *Engerix-B*, following 3 primary vaccine doses in terms of GMCs and anti-PRP concentrations ≥0.15 ug/mL and ≥1.0 ug/mL.
6. To compare the immunogenicity of *Prevnar13* co-administered with *Hiberix, Pediarix* and *Rotarix* to *Prevnar13* co-administered with *ActHIB*, *Pediarix* and *Rotarix* , following 3 primary vaccine doses in terms of immune response to 13 *S. pneumoniae* serotypes (≥0.2 ug/mL and ≥1.0 ug/mL as measured by (b) (4)).
7. To compare the seroresponse to PT, FHA and PRN in subjects receiving *Pediarix* co-administered with *Hiberix*, *Prevnar13* and *Rotarix* compared to subjects who received *Pediarix* co-administered with *ActHIB, Prevnar13* and *Rotarix*, following 3 primary vaccine doses where seroresponse is defined as the percentage of subjects showing an antibody concentration above a threshold that lead to 90% seroresponse in the control group

The study had one safety objective:

1. To evaluate the safety and reactogenicity of a 3-dose primary vaccination course of Hiberix co-administered with Pediarix, Rotarix and Prevnar13 , to that of ActHIB co-administered with Pediarix, Rotarix and Prevnar13 and that of Pentacel co-administered with Prevnar13, Rotarix and Engerix-B.

6.1.2 Design Overview

The study was a Phase III, controlled, multi-center study with three parallel groups [Hiberix, ActHIB and Pentacel]. The Hiberix group was subdivided equally by three separate lots of Hiberix.

6.1.3 Population

The study had a total vaccinated cohort of 4,003 subjects [Table 4] in a 2:2:2:1:1 ratio of Lots A, B and C of Hiberix and ActHIB and Pentacel.

Inclusion criteria:

Subjects for whom the investigator believed that their parent(s)/(LAR[s]) could and would comply with the requirements of the protocol (e.g., completion of the diary card, return for follow-up visits).

1. A male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination.
2. Written informed consent obtained from the subject's parent/LAR.
3. Healthy subjects as established by medical history and clinical examination before entering into the study.
4. Born after a gestation period of minimum 36 weeks.
5. Infants who had not received a previous dose of hepatitis B vaccine or those who have received only 1 dose of hepatitis B vaccine administered at least 30 days prior to enrolment.

Exclusion criteria:

1. Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
2. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (For corticosteroids, this meant prednisone >20mg/day, or equivalent. Inhaled and topical steroids were allowed.)
3. Planned administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of study vaccine and until 30 days after the booster dose (influenza and hepatitis A vaccines, were allowed throughout the study and routine administration(s) of measles-mumps-rubella, varicella and pneumococcal vaccines was allowed from 30 days after the last dose of primary vaccination until 30 days before the booster dose and from 30 days after the booster dose).
4. Previous vaccination against Haemophilus influenzae type b, diphtheria, tetanus, pertussis, pneumococcus, rotavirus and/or poliovirus; more than one previous dose of hepatitis B vaccine.
5. History of Haemophilus influenzae type b, diphtheria, tetanus, pertussis, pneumococcal, rotavirus, poliovirus, and hepatitis B diseases.
6. Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).
7. History of allergic disease or reactions likely to be exacerbated by any component of the vaccines, including dry natural latex rubber.
8. Major congenital defects or serious chronic illness.
9. History of any neurologic disorders or seizures.
10. Acute disease at time of enrollment. (Acute disease was defined as the presence of moderate or severe illness with or without fever). All vaccines could be administered to persons with a minor illness such as diarrhea and mild upper respiratory infection with or without low-grade febrile illness, i.e. rectal temperature <38.0°C (<100.4°F). A temperature greater than or equal to this cut-off warranted deferral of the vaccination pending recovery of the subject.
11. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
12. Concurrent participation in another clinical study, up to 30 days prior to study entry or at any time during the study period, in which the subject had been or would have been exposed to an investigational or a non-investigational product (pharmaceutical product or device).
13. Child in care.
14. History of intussusception.
15. History of uncorrected congenital malformation of the gastrointestinal tract that would have predisposed the infant to intussusception.
16. History of Severe Combined Immunodeficiency Disease (SCID).

6.1.4 Study HIB-097 Treatments or Agents Mandated by the Protocol

Each of the vaccines mandated by the study protocol is listed below with their formulations, presentation, volume/dose and lot numbers.

Vaccine	Formulation	Presentation	Volume/dose	Lot numbers
Hiberix (GSK Biologicals)	Per dose: 10mcg of purified capsular polysaccharide of Hib covalently bound to approximately (b) (4) mcg of tetanus toxoid 12.6 mg of lactose as stabilizer	White lyophilized pellet for reconstitution with sterile 0.9% saline solution Reconstituted for injection: clear, colorless liquid	0.5 mL/dose	Primary: AHIBVC243A (Lot A) AD02VB362A (Diluent Lot A) AHIBVC251A (Lot B) AD02VB363A (Diluent Lot B) AHIBVC292A (Lot C) AD02VB365A (Diluent Lot C) Booster: AHIBVC680C (Booster lot) AD02VB458A (Diluent – booster)

Vaccine	Formulation	Presentation	Volume/dose	Lot numbers
ActHIB (Sanofi Pasteur)	Per dose: 10mcg of purified capsular polysaccharide of Hib conjugated to 24mcg of inactivated tetanus toxoid 8.5% of sucrose	As provided: White lyophilized pellet for reconstitution with sterile 0.4% saline solution Reconstituted for injection: clear, colorless liquid	0.5 mL/dose	UF728AB UF633AA (Diluent)

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Vaccine	Formulation	Presentation	Volume/dose	Lot numbers
Pentacel (Sanofi Pasteur)	Per dose: diphtheria toxoid 15 Lf, tetanus toxoid 5 Lf pertussis toxin (PT) detoxified 20 mcg filamentous hemagglutinin (FHA) 20 mcg pertactin (PRN) 3 mcg fimbriae types 2 and 3 (FIM) 5 mcg Poliovirus Type 1 (Mahoney) 40 D-antigen units Poliovirus Type 2 (MEF-1) 8 D-antigen units Poliovirus Type 3 (Saukett) 32 D-antigen units PRP of *Haemophilus influenzae* type b covalently bound to 24 µg of tetanus toxoid (PRP-T) 10 mcg 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative) and <4 pg of neomycin and <4 pg polymyxin B sulfate	Reconstituted for injection: Uniform, cloudy, white to off-white (yellow tinge) suspension	0.5 mL/dose	C3472AA C3253AA

Vaccine	Formulation	Presentation	Volume/dose	Lot
Pediarix (GSK Biologicals)	Per dose: Diphtheria toxoid 25 Lf, Tetanus toxoid 10 Lf, Inactivated PT 25 FHA 25 mcg, PRN 8 mcg, HBsAg (recombinant) mcg, Poliovirus type 1 (Mahoney) 40 D units, Poliovirus type 2 8 D antigen units, Poliovirus type 3 32 D antigen units, Aluminum as more than 0.85 mg by assay, Residual formaldehyde ≤100 Polysorbate 80 ≤100 Sodium chloride 4.5 Neomycin ≤0.05 ng, Polymyxin B ≤0.01	Homogeneou turbid, white suspension	0.5 mL/dose	AC21B209C AC21B249B AC21B209C
Engerix-B (GSK Biologicals)	Per dose (pediatric formulation): surface antigen 10 (adsorbed on 0.25 mg aluminum as hydroxide), Sodium chloride 9 mg/mL, phosphate buffers (disodium phosphate dihydrate, 0.98 sodium dihydrogen phosphate dihydrate, 0.71mg/mL).	Suspension pre-filled syringe	0.5 mL/dose	AHBVB769 AHBVB796
Prevnar13 (Manufactur by Wyeth marketed by Pfizer)	Per dose: 2.2 mcg saccharide of 3, 4, 5, 6A, 7F, 9V, 18C, 19A, 19F and and 4.4 mcg of 6B conjugated to carrier protein, to aluminum	Homogeneou white suspension	0.5 mL/dose	E44526 E44520 915376

Vaccine	Formulation	Presentation	Volume/dose	Lot
Rotarix Biologicals)	Per dose: At least median Cell Culture Infective Dose live, attenuated human G1P[8] rotavirus after reconstitution.	Vial of lyophilized vaccine to be reconstituted with a liquid diluent in a prefilled oral applicator	1.0 mL/dose	A41CB30 A41FB199A A41DB199 A41CB199 A41FB036A A41DB036 A41CB036 A41FB098A A41DB008 A41CB098

6.1.5 Directions for Use

Reconstitution: HIBERIX was reconstituted with the accompanying saline diluent. The reconstituted vaccine is a clear and colorless solution.

Administration: HIBERIX was administered as a 4-dose series (0.5-mL each) given by intramuscular injection. The primary immunization series consisted of 3 doses administered at 2, 4, and 6 months of age, followed by a booster dose administered at 15 months through 4 years of age (prior to fifth birthday). The first dose could be given as early as 6 weeks of age.

6.1.6 Sites and Centers

There were 67 U.S. sites and the study was conducted under IND 14151. .

6.1.7 Surveillance/Monitoring

Table 2. List of study procedures – primary vaccination epoch, Study HIB-097

Age	6-12 weeks	4 months	6 months	7 months	12 Months
Epoch	PRIMARY				Extended Safety Follow-up (phone call
Visit	VISIT 1	VISIT 2	VISIT 3¶	VISIT 4	
Timing	Day 0	Month 2	Month 4	Month 5	Month 10
Sampling time point				BS1	
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check warnings and	●	●	●		
Check elimination criteria		●	●	●	
Check contraindications	●	●	●		
Vaccination history	●				
Medical history	●				
Physical examination†	○	○	○	○	
Pre-vaccination measurement of body	●	●	●		
Measure/record height and	●				
Blood sampling for antibody determination (6.0 mL) in subjects included in the sub- cohorts* for immunogenicity				●	
Randomization	●				
Vaccination	●	●	●		
30 min observation after vaccination	○	○	○		
Dispense diary card, measurement gauge	○	Diary card	Diary card		
Daily (within 4 days after each vaccination) post-vaccination recording of solicited symptoms AEs by subjects' parent(s)/LAR(s)	●	●	●		
Recording of any concomitant medications/vaccination	●	●	●	●	

Recording of daily post-vaccination of unsolicited AEs by subjects' parent(s)/LAR(s) (up to 30 days after each vaccination)	●	●	●		
Return of diary cards		●	●	●	
Diary cards transcription by investigator		●	●	●	
Telephone contact at the end of the 6 month safety follow-up for collection of safety data					●
Recording of any intercurrent medical	●	●	●	●	
Reporting of SAEs	●	●	●	●	●
Recording of specific adverse events‡	●	●	●	●	●
Analysis on clean data				○	○
End of safety follow-up					●

Source: adapted from sBLA 125347.231, CSR HIB-097, table 1, p.82

● was used to indicate a study procedure that required documentation in the individual eCRF.
○ was used to indicate a study procedure that did not require documentation in the individual eCRF.
¶ Visit 3 was to be conducted at least 8 weeks after Visit 2 and when the subject was at least 24 weeks of age.
†During Visit 1, physical examination was performed based on the medical history.
During Visits 2, 3 and 4, physical examination was to be performed only if the subject's parent(s)/LAR(s) indicated during questioning that there may have been some underlying pathology.
‡ Events to be reported were new onset of chronic diseases (e.g. autoimmune disorders, asthma, type I diabetes and allergies) and conditions prompting Emergency room (ER) visits.
$ At the end of the safety follow-up following the primary vaccination course, parent(s)/ LAR(s) were called by the investigator or study staff to collect information on SAEs and specific adverse events.
* A blood sample was taken at Visit 4 from all subjects included in the Sub-cohorts Hiberix A-PRP, B-PRP and C-PRP, Sub-cohorts ActHIB and Pentacel.

6.1.8 Endpoints and Criteria for Study Success

This study had six co-primary immunogenicity endpoints which are listed below along with the criteria for success. [These endpoints are enumerated again and the criteria for success defined as each endpoint is presented, in section 6.1.11, Efficacy Analyses and section 6.1.12, Safety Analyses].

1. To demonstrate lot to lot consistency of three manufacturing lots of Hiberix co-administered with Pediarix, Prevnar 13 and Rotarix, following three primary vaccine doses in terms of antibody responses to PRP [*Lot-to-lot consistency was evaluated by each pair-wise ratio of geometric mean concentrations (GMC) values for anti-PRP obtained for the 3 lots of Hiberix (Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP). The criterion for lot-to-lot consistency was that the two-sided 95% confidence limits on the anti-PRP GMC ratio between lots were within the [0.67; 1.5] interval for all 3 pair-wise comparisons.*

2. To demonstrate non-inferiority of Hiberix to ActHIB in terms of anti-PRP antibody concentration ≥1.0ug/mL [*Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥1.0 ug/mL was ≥ -10% (clinical limit for non-inferiority).*

3. To demonstrate non-inferiority of Hiberix to ActHIB in terms of anti-PRP antibody concentration ≥0.15ug/mL [*Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥0.15 ug/mL was ≥ - 5% (clinical limit for non-inferiority).*

4. To demonstrate non-inferiority of Pediarix co-administered with Hiberix, Prevnar 13 and Rotarix to Pediarix co-administered with ActHIB, Prevnar 13 and Rotarix, in terms of immune responses to diphtheria, tetanus, pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN] and to poliovirus types 1,2 and 3 [*Lower limit of the standardized asymptotic 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) in the percentages of subjects with seroprotective concentrations (≥0.1 IU/mL) of anti-diphtheria and anti-tetanus antibodies was ≥ -10% (clinical limit for non-inferiority)*

and

Lower limit of the 97.5% CIs on the GMC ratios (Subset Pertussis Co-Ad divided by Sub cohort ActHIB) for antibodies to each of the pertussis antigens (PT, FHA and PRN) was ≥0.67 (clinical limit for non-inferiority)

and

limit of the standardized asymptotic 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) in the percentages of

subjects with seroprotective titers (≥8) of antibodies to each of the poliovirus antigens was ≥ -5% (clinical limit for non-inferiority).

and

Lower limit of the standardized asymptotic 97.5% CIs on the percentage of subjects (Subset Hiberix Co-Ad) with seroprotective titers (≥8) of antibodies to each of the poliovirus antigens was ≥90%.

5. To demonstrate the non-inferiority of a three dose series of Prevnar 13 co-administered with Hiberix, Rotarix and Pediarix compared to that of Prevnar 13 co-administered with ActHIB, Rotarix and Pediarix, in terms of *S. pneumonia* GMCs by (b) (4) . [*Lower limits of the two-sided 97.5% CIs on the GMC ratio (Subset Hiberix Co-Ad over Sub cohort ActHIB) for each S. pneumoniae serotype (1 [anti-1], 3 [anti-3], 4 [anti-4], 5 [anti-5], 6A [anti-6A], 6B [anti-6B], 7F [anti-7F], 9V [anti-9V], 14 [anti-14], 18C [anti-18C], 19A [anti-19A], 19F [anti-19F] and 23F [anti-23F]) were ≥ 0.5 (clinical limit for noninferiority)*

6. To rule out a 10% decrease in sero-response to PT, FHA and PRN in subjects who received Pediarix co-administered with Hiberix, Prevnar 13 and Rotarix compared to subjects who received Pediarix co-administered with ActHIB, Prevnar 13 and Rotarix, by the criteria of percentage of subjects showing an antibody concentration above a threshold that leads to 95% sero-response in the control group. [*P-value on the difference in seroresponse between groups was <1.25% for each PT, FHA and PRN antigen (p-value was computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the Subset Pertussis Co-Ad was <85% and the a-posteriori probability of the cut-off in the Sub-cohort ActHIB).*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review for a detailed discussion of the statistics used in the analysis of Study HIB-097. Please refer to Section 4.5, above.
Statistical analyses of the primary objectives were performed in a hierarchical manner, as follows: lot to lot consistency of three lots of Hiberix; non-inferiority of Hiberix compared to ActHIB one month after 3 primary vaccination series (administered at ages 2, 4 and 6 months) in terms of anti-PRP antibody concentration ≥ 1.0/ug/mL and ≥0.15ug/mL; and non-inferiority of immune responses to antigens contained in co-administered vaccines (diphtheria and tetanus, pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), poliovirus types 1,2 and 3, and thirteen pneumococcal serotypes*).*
The statistical methodology was appropriate for the multiple co-primary endpoints of the study. Lot to lot consistency needs to be established first to determine that anti-PRP antibody results are consistent across lots. Non-inferiority to ActHIB is critical to the determination that the clinical efficacy of Hiberix is likely to be non-

inferior to ActHIB. Hiberix will most often be administered simultaneously with diphtheria, tetanus, pertussis, polio and pneumococcal vaccines so that it is important to demonstrate non-interference with the immune responses to those co-administered antigens.

6.1.10 Study Population and Disposition

The study population and disposition of subjects are presented in Table 3. Study cohorts were defined as follows:

Primary Total Vaccinated cohort

The Primary Total Vaccinated cohort (Prim-TVC) included all vaccinated subjects. For the Prim-TVC analysis of safety, this included all subjects with at least one vaccine administration documented. For the Prim-TVC analysis of immunogenicity, this included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The Prim-TVC analysis was performed per treatment actually administered at the first dose in the primary vaccination epoch.

Primary According-to-protocol (ATP) cohort for safety

The Primary ATP cohort for safety included all eligible subjects: who met all inclusion criteria and no exclusion criteria for the study;
who received at least 1 dose of study/control vaccine according to their treatment.
assignment during the primary vaccination course; for whom the injection site of study/control vaccine was known; who did not receive a vaccine not specified or forbidden in the protocol during the primary vaccination course, i.e. up to the post-dose 3 blood sample.

Primary ATP cohort for immunogenicity

The Primary ATP cohort for immunogenicity included all evaluable subjects (i.e. those who met all eligibility criteria, complied with the procedures defined in the protocol, with no elimination criteria during the study) from the Primary ATP cohort for safety to whom 3 vaccine doses were administered and assay results were available for antibodies against at least one antigen for the blood sample taken one month after the third vaccine dose.

Table 3. Study HIB-097, Population and Disposition of Subjects

Number of subjects	*Hiberix*	*ActHIB*	*Pentacel*
Planned, N	3000	500	500
Randomized, N (Total Vaccinated Cohort)	2963	520	520
Completed to Visit 4, n (%)	2625 (88.6)	470 (90.4)	457 (87.9)
Completed to, ESFU CONTACT for primary epoch n (%)	2706 (91.3)	487 (93.7)	472 (90.8)
Demographics	*Hiberix*	*ActHIB*	*Pentacel*
N (Total Vaccinated Cohort)	2963	520	520
Females: Males	1424:1539	271:249	258:262
Mean Age, weeks (SD)	8.6 (1.08)	8.6 (1.13)	8.7 (1.12)
White - Caucasian / European heritage, n (%)	1757 (59.3)	324 (62.3)	314 (60.4)

	Hiberix	*ActHIB*	*Pentacel*
Reasons for withdrawal :			
Subject died	0	0	0
Serious Adverse Event	0	0	0
Non-Serious Adverse Event	0	0	0
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0
Protocol violation	0	0	2
Consent withdrawal (not due to an adverse event)	3	1	1
Migrated/moved from study area	7	1	1
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	33	4	6
Sponsor study termination	0	0	0
Others	24	6	4

Source: adapted from sBLA 125347.231, CSR HIB-097, table 27, p. 196

Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with Infanrix
ActHIB = *ActHIB* co-administered with Infanrix
Pentacel = *Pentacel*
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed visit 6
Withdrawn = number of subjects who did not come for the visit 6

Clinical Reviewer's Comment: In general there were six times as many subjects in the Hiberix as compared to either the ActHIB or the Pentacel groups, and taking this into account there was balance between the groups in terms of completion rates, lost to follow up and protocol deviations. Therefore the subject disposition data would not suggest any bias in the study results by any of these parameters.

6.1.10.1 Populations Enrolled/Analyzed

Table 4 shows the numbers of subjects enrolled into the study, the number excluded from ATP analysis and the reasons for the exclusions. Overall the Hiberix group represented 75% of all enrolled subjects, and the ActHIB and Pentacel groups each represented 12.5% of all enrolled subjects.

Table 4. Number of subjects enrolled into Study HIB-097 as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	Total			***Hiberix***		***ActHIB***		***Pentacel***	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total Cohort	**4009**			**2968**		**521**		**520**	
Study vaccine dose not administrated but subject number allocated	6	6		5	5	1	1	0	0
Total Vaccinated cohort	**4003**		**100**	**2963**		**520**		**520**	
Administration of vaccine(s) forbidden in the protocol	47	47		34	34	7	7	6	6
Randomization failure	3	3		0	0	0	0	3	3
Randomization code broken at the investigator site	3	3		3	3	0	0	0	0
Study vaccine dose not administered	44	59		11	19	1	6	32	34
Others (reacto)	11	13		10	11	1	1	0	1
ATP cohort for safety	**3895**		**97.3**	**2905**		**511**		**479**	
Administration of any medication forbidden	3	4		0	1	2	2	1	1
Concomitant infection not related to the vaccine which may influence immune response	5	7		4	5	0	0	1	2
Noncompliance with vaccination schedule (including wrong and unknown dates)	122	124		87	89	16	16	19	19
Noncompliance with blood sampling schedule (including wrong and unknown dates)	119	130		93	100	12	12	14	18
Essential serological data missing	412	471		319	36	48	55	45	55
Blood sample available but not yet tested (interim analysis)	2	2		2	2	0	0	0	0
Subject not planned to be bled for their all blood sampling visits	1112	1187		808	853	158	168	146	166
ATP cohort for immunogenicity	**2120**		**53.0**	**1592**		**275**		**253**	

Source: adapted from sBLA 125347.231, CSR HIB-097, table 35, p.203
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
Pentacel = *Pentacel* co-administered with *Prevnar13*, *Engerix-B* and *Rotarix*
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated cohort

Clinical Reviewer's Comment: The numbers of subjects excluded from the ATP analyses were proportional between the three groups and are not expected to have an influence on the overall validity of the study conclusions. 53% of the total vaccinated cohort were in the immunogenicity subset and 54% of HIberix subjects, 53% of ActHIB subjects and 49% of Pentacel subjects were in the immunogenicity subset. Seventy percent of all subjects were randomly selected for the immunogenicity sub-cohort for each study group. The reasons for exclusion from the ATP immunogenicity analyses were non-compliance with the vaccination schedule, non-compliance with blood sampling and essential serological data missing and were proportionately distributed between the three study groups.

6.1.10.1.1 Demographics

Table 5. Summary of demographic characteristics (Primary Total Vaccinated Cohort): Study HIB-097

		Hiberix **N =**		***ActHIB*** **N = 520**		***Pentacel***		**Total N =**	
Characteristics	**Parameters or Categories**	**Value**	**%**	**Value**	**%**	**Value**	**%**	**Value**	**%**
Age[W]	Mean	8.6	-	8.6	-	8.7	-	8.6	-
	SD	1.08	-	1.13	-	1.12	-	1.09	-
	Median	9.0	-	9.0	-	9.0	-	9.0	-
	Minimum	5	-	6	-	6	-	5	-
	Maximum	13	-	13	-	12	-	13	-
Height[cm]	Mean	58.5	-	58.2	-	58.5	-	58.4	-
	SD	3.37	-	3.03	-	3.13	-	3.30	-
	Median	58 0	-	58 0	-	58 0	-	58 0	-
	Minimum	28	-	41	-	51	-	28	-
	Maximum	89	-	76	-	86	-	89	-
Weight[Kg]	Mean	5.4	-	5.3	-	5.4	-	5.4	-
	SD	0.71	-	0.70	-	0.65	-	0.70	-
	Median	5.3	-	5.3	-	5.4	-	5.3	-
	Minimum	3	-	3	-	3	-	3	-
	Maximum	8	-	8	-	8	-	8	-
Gender	Female	142	48.	271	52.	258	49.	195	48.
	Male	153	51.	249	47.	262	50.	205	51.
Race	African heritage / African	284	9.6	45	8.7	51	9.8	380	9.5
	American Indian or Alaskan	253	8.5	39	7.5	46	8.8	338	8.4
	Asian - Central / South	62	2.1	9	1.7	12	2.3	83	2.1
	Asian - East Asian heritage	36	1.2	7	1.3	5	1.0	48	1.2
	Asian - Japanese heritage	14	0.5	3	0.6	1	0.2	18	0.4
	Asian - South East Asian	120	4.0	24	4.6	22	4.2	166	4.1
	Native Hawaiian or other	23	0.8	4	0.8	4	0.8	31	0.8
	White - Arabic / North	29	1.0	4	0.8	1	0.2	34	0.8
	White - Caucasian /	175	59.	324	62.	314	60.	239	59.
	Other	385	13	61	11	64	12	510	12
Hepatitis B Vaccine at Birth	No	215	7.3	48	9.2	33	6.3	296	7.4
	Yes	2744	92.6	472	90.8	487	93.7	3703	92.5

Source: adapted from sBLA 125347.231, CSR HIB-097, table 48, p.212

Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
Pentacel = *Pentacel* co-administered with *Prevnar13*, *Engerix-B* and *Rotarix*
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Age [W] = age expressed in Weeks

Clinical Reviewer's Comment: The enrolled populations in each study group were equally balanced for sex and the proportion of subjects by race/ethnicity; the demographic characteristics of the study population overall is a reasonable approximation of the diversity in the U.S. population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please refer to Table 3 in section 6.1.10.1.1 Demographics.

6.1.11 Efficacy Analyses

The efficacy analyses is divided by co-primary and secondary endpoint analyses. There were six co-primary endpoints and seven secondary endpoints and each is stated in order, followed by the data from the study relevant to the endpoint and clinical reviewer comments. Seventy percent of all enrolled subjects were randomized to the immunogenicity sub-cohort in each study group and this sub-cohort was the basis for evaluation of each co-primary endpoint.
The first co-primary endpoint was: To demonstrate the lot-to-lot consistency of 3 manufacturing lots of Hiberix co-administered with Pediarix, Prevnar13 and Rotarix following 3 primary vaccine doses in terms of immune response to polyribosylribitol phosphate (PRP).
Criteria for lot-to-lot consistency: (1 month after last dose of primary vaccination): Lot-to-lot consistency was evaluated by each pair-wise ratio of geometric mean concentrations (GMC) values for anti-PRP obtained for the 3 lots of Hiberix (Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP). The criterion for lot-to-lot consistency was that the two-sided 95% confidence limits on the anti-PRP GMC ratio between lots were within the [0.67; 1.5] interval for all 3 pair-wise comparisons.

Table 6. Study HIB-097: GMC ratio (between *Hiberix* lots) of anti-PRP one month after primary vaccination (Primary ATP cohort for immunogenicity)

						GMC ratio			
								95% CI	
Group description	**N**	**GMC**	**Group description**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Hiberix Lot A	527	4.994	*Hiberix* Lot B	537	6.323	*Hiberix* Lot A /*Hiberix* Lot B	0.790	**0.641**	**0.974**
Hiberix Lot A	527	4.994	*Hiberix* Lot C	526	4.416	*Hiberix* Lot A /*Hiberix* Lot C	1.131	**0.916**	**1.396**
Hiberix Lot B	537	6.323	*Hiberix* Lot C	526	4.416	*Hiberix* Lot B /*Hiberix* Lot C	1.432	**1.161**	**1.765**

Source: adapted from sBLA 125347.231, CSR HIB-097, table 55, p. 219
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (ANOVA model - pooled variance of the three groups in the comparison); LL = lower limit, UL = upper limit

Non-inferiority criteria: The criterion for lot-to-lot consistency was that the two-sided 95% confidence limits on the anti-PRP GMC ratio between lots were within the [0.67; 1.5] interval for all 3 pair-wise comparisons.

Clinical Reviewer's Comment: *In this reviewer's opinion the failure to meet this first co-primary endpoint on lot to lot consistency is due to the higher GMC for Lot B, which resulted in the 95% CI for the LL of the ratio between Lot A to Lot B to be 0.64 [less than the 0.67 LL criteria] and the ratio between Lot B to Lot C UL to be 1.76 [higher than the 1.5 criteria]. However the magnitude by which lot consistency was missed is not likely to be clinically significant. Therefore the subsequent analyses of anti-PRP antibody levels and antibody levels against co-administered antigens may proceed under the assumption that Lots A, B and C were clinically similar and the GMC titers obtained for each lot were sufficient to induce protection from invasive Hib disease.*

The second co-primary endpoint was: To demonstrate the non-inferiority of Hiberix to ActHIB, each co-administered with Pediarix, Prevnar13 and Rotarix, following 3 primary vaccine doses in terms of anti-PRP antibody concentration ≥1.0 ug/mL.
Criterion for non-inferiority (1 month after last dose of primary vaccination): Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Sub-cohort

ActHIB) in the percentage of subjects with anti-PRP concentrations ≥1.0 ug/mL was ≥-10% (clinical limit for non-inferiority).
The third co-primary endpoint was: To demonstrate the non-inferiority of Hiberix to ActHIB, each co-administered with Pediarix, Prevnar13 and Rotarix, following 3 primary vaccine doses in terms of anti-PRP antibody concentrations ≥0.15 ug/mL
Criterion for non-inferiority (1 month after last dose of primary vaccination): Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥0.15 ug/mL was ≥-5% (clinical limit for non-inferiority).

Tables 7 and 8 present the immune response data relevant to the second and third co-primary endpoints, the percentage of subjects achieving anti-PRP antibody levels ≥0.15ug/ml and ≥1.0ug/ml, one month after primary series. Table 7 shows comparisons between Hiberix and ActHIB and Table 8 shows comparisons between Hiberix, ActHIB and Pentacel.

Table 7. Study HIB-097: Difference between groups (*Hiberix* and *ActHIB*) in percentage of subjects with antibody concentration ≥ 0.15 ug/mL, ≥ 1.0 ug/mL to PRP by (b) (4) one month after primary vaccination (Primary ATP cohort for immunogenicity)

								Difference in percentage (*Hiberix* minus *ActHIB*)		
		Hiberix			***ActHIB***				**95% CI**	
Antibody	**Cut-off**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
Anti-PRP	0.15 µg/mL	1590	1536	**96.6**	274	265	**96.7**	-0.11	**-1.98**	**2.82**
	1 µg/mL	1590	1291	**81.2**	274	246	**89.8**	-8.59	**-12.28**	**-4.07**

Source: adapted from sBLA 125347.231, CSR HIB-097, table 56, p.219
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Non-inferiority criteria: Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥1.0 µg/mL was ≥-10% (clinical limit for non-inferiority).

Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥0.15 μg/mL was ≥-5% (clinical limit for non-inferiority).

Clinical Reviewer's Comment: Non-inferiority criteria were not met for primary objective #2 since the LL of the 95% CI for the difference in the percentage of subjects with anti-PRP concentration ≥1.0 ug/mL (Hiberix group compared to ActHIB group) was -12.8%, which was lower than the predefined NI margin (≥ -10.0%). 81.2% of Hiberix subjects and 89.8% of ActHIB subjects achieved an anti-PRP antibody concentration of ≥1.0 ug/mL. The statistical significant difference in anti-PRP antibody response is unlikely to affect the relative efficacy of Hiberix compared to ActHIB.

The relationship between anti-PRP Ab levels and protection from invasive Hib disease is well recognized from the published literature [Ref 1]. A minimum anti-PRP level of ≥ 0.15ug/mL was necessary for short-term protection from invasive Hib disease and that levels ≥ 1.0ug/mL correlated with protection from invasive Hib disease for up to one year post primary series [Ref. 1]. Use of anti-PRP antibodies as a serological marker of protection to infer effectiveness of Hib conjugate vaccines is an acceptable regulatory approach and has been used to infer effectiveness of other Hib conjugate vaccines.

Table 8. Study HIB-097: Percentage of subjects with anti-PRP antibody concentrations greater than or equal to 0.15 ug/mL, greater than or equal to 1.0 ug/mL and geometric mean concentration (GMC) by group and gender one month after primary vaccination (Primary ATP cohort for immunogenicity)

					≥ 0.15 μg/mL				≥ 1 μg/mL				GMC		
							95% CI				95% CI			95% CI	
3 and 114	group	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	valu	LL	UL
Anti-PRP	Male	*Hiberix*	POS 3	833	801	**96.2**	**94.6**	97.4	661	**79**	**76**	82	4.56	4.04	5.14
		ActHIB	POS 3	125	120	**96.0**	**90.9**	98.7	112	**89**	**82**	94	6.99	5.27	9.27
		Pentacel	POS 3	136	123	**90.4**	**84.2**	94.8	102	**75**	**66**	82	3.54	2.52	4.98
	Female	*Hiberix*	POS 3	757	735	**97.1**	**95.6**	98.2	630	**83**	**80**	85	5.98	5.30	6.76
		ActHIB	POS 3	149	145	**97.3**	**93.3**	99.3	134	**89**	**83**	94	6.54	5.08	8.41
		Pentacel	POS 3	117	111	**94.9**	**89.2**	98.1	96	**82**	**73**	88	3.75	2.76	5.11

Source: adapted from sBLA 125347.231, CSR HIB-097, table 65, p.226
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix Pentacel* = *Pentacel* co-administered with *Prevnar13*, *Engerix-B* and *Rotarix* GMC = geometric mean antibody concentration calculated on all subjects
POS 3 = one month post dose 3
N = number of subjects with available results

n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Clinical Reviewer's Comment: Analyses of anti-PRP responses following Pentacel, which is a U.S. licensed vaccine containing a Hib component, were exploratory. Nonetheless, the numbers of subjects in the Pentacel group were the same as in the ActHIB group. The percentages of subjects with anti-PRP antibody titers ≥0.15ug/mL and the percentages of subjects with anti-PRP antibody titers ≥1.0ug/mL were higher after the third dose of Hiberix than after the third dose of Pentacel. In this reviewer's opinion, these data are supportive of acceptable inferred effectiveness of Hiberix in the intended age group.

Table 9 presents the data for anti-PRP antibody responses one month before the booster dose.

Table 9. Study HIB-097: Percentage of subjects with anti-PRP antibody concentrations greater than or equal to 0.15 µg/mL, greater than or equal to 1.0 µg/mL and geometric mean concentrations (GMC) by group before the booster dose of Hib (Booster ATP cohort for immunogenicity)

				≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PRP	*Hiberix*	PRE	329	247	75.1	70.0	79.7	106	32.2	27.2	37.6	0.498	0.422	0.588
	ActHIB	PRE	226	172	76.1	70.0	81.5	61	27.0	21.3	33.3	0.467	0.385	0.567
	Pentacel	PRE	175	116	66.3	58.8	73.2	44	25.1	18.9	32.2	0.380	0.299	0.484

Source: adapted from sBLA 125347.231, CSR HIB-097, table 127, p. 292
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Infanrix*
ActHIB = *ActHIB* co-administered with *Infanrix*
Pentacel = *Pentacel*
GMC = geometric mean antibody concentration, calculated for all subjects. Antibody concentrations below the cut-off of the assays were assigned a value of one half the cut-off for the purpose of calculating the GMC
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-booster vaccination

Reviewer Comment: The percentage of subjects with an anti-PRP concentration ≥0.15ug/mL before the booster dose was higher in the Hiberix group (75.1%) than in the Pentacel group (66.3%); and the percentage of subjects with an anti-PRP concentration ≥1.0ug/mL prior to the booster dose was 32.2% in the Hiberix group and 25.1% in the Pentacel group. Also, the percentages of subjects with an anti-PRP concentration ≥0.15ug/mL prior to the booster dose were similar among the Hiberix and ActHIB groups. In this reviewer's opinion, the data are supportive of acceptable inferred effectiveness of Hiberix in the intended age group. This data represents an exploratory analysis and was not a pre-specified primary endpoint for efficacy in this study.

Tables 10 to 15 present the immune responses to antigens in concomitantly administered vaccines, measured at 7 months of age, when given with Hiberix or ActHib.

Table 10. Study HIB-097: Difference between groups (*Hiberix* and *ActHIB*) in percentage of subjects with antibody concentration ≥ 0.1 IU/mL to D, T by (b) (4) **one month after primary vaccination (Primary ATP cohort for immunogenicity)**

								Difference in percentage (*Hiberix* minus *ActHIB*)		
		Hiberix			***ActHIB***				**97.5% CI**	
Antibody	**Cut-off**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
Anti-D	0.1 IU/ml	393	393	**100**	273	273	**100**	0.00	**-1.26**	1.81
Anti-T	0.1 IU/ml	393	393	**100**	274	274	**100**	0.00	**-1.26**	1.80

Source: adapted from sBLA 125347.231, CSR HIB-097, table 57, p.220
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
N = number of subjects with available results
% = percentage of subjects anti-T/anti-D concentration ≥ 0.1 IU/mL
97.5% CI = Standardized asymptotic 97.5% confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criteria: The lower limit of the standardized asymptotic 97.5% CIs on the differences (Subset *Hiberix* Co-Ad minus Sub-cohort *ActHIB*) in the percentages of subjects with seroprotective concentrations (≥0.1 IU/mL) of anti-diphtheria and anti-tetanus antibodies greater than -10% (clinical limit for non-inferiority).

Clinical Reviewer's Comment: 100% of Hiberix subjects achieved the anti-T and anti-D concentration ≥ 0.1 IU/mL and met the criteria for non-inferiority to ActHIB since the difference in percentages of subjects with sero-protective concentrations was greater than -10%.

Table11. Study HIB-097: GMC ratio (*Hiberix* over *ActHIB*) of anti-PT, FHA and PRN one month after primary vaccination (Primary ATP cohort for immunogenicity)

					GMC ratio (*Hiberix* / *ActHIB*)		
	Hiberix		***ActHIB***			**97.5% CI**	
Antibody	**N**	**GMC**	**N**	**GMC**	**Value**	**LL**	**UL**
Anti-PT ((b) (4))	792	73.2	275	71.9	1.017	**0.918**	1.127
Anti-FHA ((b) (4)	791	321.8	275	295.8	1.088	**0.983**	1.204
Anti-PRN ((b) (4)	789	111.6	275	93.5	1.193	**1.030**	1.382

Source: adapted from sBLA 125347.231, CSR HIB-097, table 58, p.220
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
GMC = Geometric mean antibody concentration obtained from an ANOVA model (pooled variance from 2 groups)
N = Number of subjects with post-vaccination results available
97.5% CI = 97.5% confidence interval for the GMC ratio; LL = lower limit, UL = upper limit
Non-inferiority criteria: The lower limit of the 97.5% CIs on the GMC ratios (Subset Pertussis Co-Ad divided by Sub-cohort *ActHIB*) for antibodies to each of the pertussis antigens (PT, FHA and PRN) is greater than 0.67 (clinical limit for non-inferiority).

Clinical Reviewer's Comment: The lower limit of the 97.5% CIs on the GMC ratios (Subset Pertussis Co-Ad divided by Sub-cohort ActHIB) for antibodies to each of the pertussis antigens (PT, FHA and PRN) was 0.918, 0.983 and 1.030 respectively, which was greater than 0.67 (clinical limit for non-inferiority).

Table 12. Study HIB-097: Difference between groups (*Hiberix* and *ActHIB*) in percentage of subjects with antibody titer ≥ 8 to Anti-Polio-1, 2, 3, one month after primary vaccination (Primary ATP cohort for immunogenicity)

								Difference in percentage (*Hiberix* minus *ActHIB*)		
		Hiberix			***ActHIB***				**97.5% CI**	
Antibody	**Cut-off**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
Anti-Polio 1	8 ED50	248	246	**99.2**	181	181	**100**	-0.81	**-3.38**	1.91
Anti-Polio 2	8 ED50	280	275	**98.2**	192	188	**97.9**	0.30	**-2.84**	4.28
Anti-Polio 3	8 ED50	257	254	**98.8**	181	181	**100**	-1.17	**-3.87**	1.55

Source: adapted from sBLA 125347.231, CSR HIB-097, table 59, p.220
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
N = number of subjects with available results
% = percentage of subjects with anti-polio titers ≥8
97.5% CI = Standardized asymptotic 97.5% confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criteria: *The lower limit of the 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) for in the percentage of subjects with antibody titers ≥8 to each of the poliovirus antigens (type 1, type 2 and type 3) is greater than -5% (clinical limit for non-inferiority).*

Clinical Reviewer's Comment: The lower limit of the 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) for in the percentage of subjects with antibody titers ≥8 to each of the poliovirus antigens (type 1, type 2 and type 3) was -3.38%, -2.84% and -3.87%, which was greater than -5% (clinical limit for non-inferiority).

Table 13. Study HIB-097: GMC ratio (*Hiberix* over *ActHIB*) of anti-pneumococcal (13 serotypes) antibody concentration one month after primary vaccination (Primary ATP cohort for immunogenicity)

					GMC ratio (*Hiberix* / *ActHIB*)		
	Hiberix		***ActHIB***			**97.5% CI**	
Antibody	**N**	**GMC**	**N**	**GMC**	**Value**	**LL**	**UL**
Anti-Pneumoniae 1 (µg/mL)	384	2.515	268	2.500	1.006	**0.873**	1.159
Anti-Pneumoniae 3 (µg/mL)	382	1.056	269	1.008	1.048	**0.921**	1.192
Anti-Pneumoniae 4 (µg/mL)	389	1.804	268	1.803	1.001	**0.886**	1.130
Anti-Pneumoniae 5 (µg/mL)	379	3.729	266	3.656	1.020	**0.874**	1.190
Anti-Pneumoniae 6A (µg/mL)	381	3.442	267	3.340	1.031	**0.894**	1.188
Anti-Pneumoniae 6B (µg/mL)	383	1.065	267	0.994	1.072	**0.871**	1.320
Anti-Pneumoniae 7F (µg/mL)	386	4.518	269	4.115	1.098	**0.964**	1.251

					GMC ratio (*Hiberix* / *ActHIB*)		
	Hiberix		***ActHIB***			**97.5% CI**	
Antibody	**N**	**GMC**	**N**	**GMC**	**Value**	**LL**	**UL**
Anti-Pneumoniae 9V (µg/mL)	386	2.516	270	2.431	1.035	**0.890**	1.204
Anti-Pneumoniae 14 (µg/mL)	384	4.506	267	4.111	1.096	**0.929**	1.294
Anti-Pneumoniae 18C (µg/mL)	380	3.655	267	3.507	1.042	**0.900**	1.207
Anti-Pneumoniae 19A (µg/mL)	384	1.556	266	1.553	1.001	**0.859**	1.167
Anti-Pneumoniae 19F (µg/mL)	384	2.745	268	2.833	0.969	**0.855**	1.098
Anti-Pneumoniae 23F (µg/mL)	384	2.046	268	1.985	1.031	**0.862**	1.232

Source: adapted from sBLA 125347.231, CSR HIB-097, table 61, p.221
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
GMC = Geometric mean antibody concentration obtained from an ANOVA model (pooled variance from 2 groups)
N = Number of subjects with post-vaccination results available
97.5% CI = 97.5% confidence interval for the GMC ratio; LL = lower limit, UL = upper limit
Non-inferiority criteria: Non-inferiority criteria: *The lower limit of the 97.5% CIs on the GMC ratios (Subset Hiberix Co-Ad over Sub-cohort ActHIB) for each S. pneumoniae serotype (anti-1, anti-3, anti-4, anti-5, anti-6A, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti-19A, anti-19F and anti-23F) is greater than 0.5 (clinical limit for non-inferiority).*

Clinical Reviewer's Comment: The lower limit of the 97.5% CIs on the GMC ratios (Subset Hiberix Co-Ad over Sub-cohort ActHIB) for each S. pneumoniae serotype (anti-1, anti-3, anti-4, anti-5, anti-6A, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti-19A, anti-19F and anti-23F) was at least 0.8, which was greater than 0.5 (clinical limit for non-inferiority).

Table 14. Study HIB-097: Percentage of subjects with anti-Polio 1,2,3 antibody titers greater than or equal to 8 and geometric mean titers (GMT) by group one month after primary vaccination (Primary ATP cohort for immunogenicity)

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-Polio 1	*Hiberix*	POS 3 M 5	248	246	**99.2**	**97.1**	99.9	604.654	513.966	711.343
	ActHIB	POS 3 M 5	181	181	**100**	**98.0**	100	663.094	547.349	803.315
	Pentacel	POS 3 M 5	175	164	**93.7**	**89.0**	96.8	135.816	107.042	172.324
Anti-Polio 2	*Hiberix*	POS 3 M 5	280	275	**98.2**	**95.9**	99.4	499.472	418.270	596.438
	ActHIB	POS 3 M 5	192	188	**97.9**	**94.8**	99.4	409.392	333.959	501.863
	Pentacel	POS 3 M 5	189	183	**96.8**	**93.2**	98.8	221.428	180.126	272.199
Anti-Polio 3	*Hiberix*	POS 3 M 5	257	254	**98.8**	**96.6**	99.8	1110.458	930.452	1325.289
	ActHIB	POS 3 M 5	181	181	**100**	**98.0**	100	1120.243	931.092	1347.821
	Pentacel	POS 3 M 5	169	168	**99.4**	**96.7**	100	304.956	242.069	384.182

Source: adapted from sBLA 125347.231, CSR HIB-097, table 75, p.239
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
Pentacel = *Pentacel* co-administered with *Prevnar13*, *Engerix-B* and *Rotarix*
GMT = geometric mean titer concentration, calculated for all subjects. Antibody titers below the cut-off of the assays were given an arbitrary value of one half the cut-off for the purpose of calculating the GMT
POS 3 M 5 = one month post dose 3 at Month 5
N = number of subjects with available results
n/% = number/percentage of subjects with antibody titers above the specified cut-off
95% CI; LL, UL = exact 95% confidence interval; lower and upper limits

Clinical Reviewer's Comment: Percentage of subjects with anti-Polio 1,2,3 antibody titers greater than or equal to 8 was 98-100% for all three groups. This was not a co-primary endpoint but rather a quantitative assessment of anti-Polio immune titers by the criteria of ≥ 8 ED50.

Table 15. Study HIB-097: Percentage of subjects with anti-*S.pneumoniae* antibody (13 serotypes) concentration greater than or equal to 0.05 ug/mL, greater than or equal to 0.2 ug/mL and greater than or equal to 1.0 ug/mL and geometric mean concentration (GMC) by group one month after primary vaccination (Primary TVC immunogenicity sub cohort)

			≥ 0.05 ug/mL				≥ 0.2 ug/mL				≥ 1.0 ug/mL				GMC		
					95% CI				95% CI				95% CI			95% CI	
Antibody	**Group**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-Pneumoniae 1	*Hiberix*	422	422	100.0	99.1	100.0	420	99.5	98.3	99.9	369	87.4	83.9	90.4	2.521	**2.334**	2.723
	ActHIB	288	288	100.0	98.7	100.0	287	99.7	98.1	100.0	256	88.9	84.7	92.3	2.526	**2.306**	2.766
	Pentacel	285	285	100.0	98.7	100.0	284	99.6	98.1	100.0	245	86.0	81.4	89.8	2.434	**2.196**	2.697
Anti-Pneumoniae 14	*Hiberix*	421	421	100.0	99.1	100.0	418	99.3	97.9	99.9	394	93.6	90.8	95.7	4.559	**4.172**	4.983
	ActHIB	288	288	100.0	98.7	100.0	286	99.3	97.5	99.9	271	94.1	90.7	96.5	4.289	**3.849**	4.780
	Pentacel	283	283	100.0	98.7	100.0	280	98.9	96.9	99.8	261	92.2	88.5	95.1	4.011	**3.574**	4.501
Anti-Pneumoniae 18C	*Hiberix*	418	418	100.0	99.1	100.0	414	99.0	97.6	99.7	398	95.2	92.7	97.1	3.685	**3.389**	4.007
	ActHIB	289	289	100.0	98.7	100.0	289	100.0	98.7	100.0	277	95.8	92.9	97.8	3.578	**3.269**	3.915
	Pentacel	282	282	100.0	98.7	100.0	281	99.6	98.0	100.0	263	93.3	89.7	95.9	3.386	**3.041**	3.770
Anti-Pneumoniae 19A	*Hiberix*	422	421	99.8	98.7	100.0	417	98.8	97.3	99.6	317	75.1	70.7	79.2	1.554	**1.437**	1.681
	ActHIB	287	286	99.7	98.1	100.0	280	97.6	95.0	99.0	217	75.6	70.2	80.5	1.590	**1.432**	1.766
	Pentacel	283	282	99.6	98.0	100.0	271	95.8	92.7	97.8	186	65.7	59.9	71.2	1.298	**1.163**	1.450
Anti-Pneumoniae 19F	*Hiberix*	423	423	100.0	99.1	100.0	422	99.8	98.7	100.0	393	92.9	90.0	95.2	2.751	**2.568**	2.948
	ActHIB	289	289	100.0	98.7	100.0	288	99.7	98.1	100.0	274	94.8	91.6	97.1	2.873	**2.654**	3.109
	Pentacel	286	286	100.0	98.7	100.0	285	99.7	98.1	100.0	266	93.0	89.4	95.7	2.515	**2.318**	2.729
Anti-Pneumoniae 23F	*Hiberix*	421	421	100.0	99.1	100.0	413	98.1	96.3	99.2	323	76.7	72.4	80.7	2.022	**1.834**	2.229
	ActHIB	288	287	99.7	98.1	100.0	285	99.0	97.0	99.8	223	77.4	72.2	82.1	2.035	**1.815**	2.281
	Pentacel	285	283	99.3	97.5	99.9	269	94.4	91.0	96.8	211	74.0	68.5	79.0	1.702	**1.484**	1.951
Anti-Pneumoniae 3	*Hiberix*	422	422	100.0	99.1	100.0	419	99.3	97.9	99.9	211	50.0	45.1	54.9	1.066	**0.988**	1.151
	ActHIB	289	289	100.0	98.7	100.0	287	99.3	97.5	99.9	154	53.3	47.4	59.2	1.025	**0.950**	1.106

			≥ 0.05 ug/mL				≥ 0.2 ug/mL				≥ 1.0 ug/mL				GMC		
					95% CI				95% CI				95% CI			95% CI	
Antibody	**Group**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
	Pentacel	286	284	99.3	97.5	99.9	283	99.0	97.0	99.8	160	55.9	50.0	61.8	1.160	**1.048**	1.283
Anti-Pneumoniae 4	*Hiberix*	428	428	100.0	99.1	100.0	428	100.0	99.1	100.0	350	81.8	77.8	85.3	1.803	**1.690**	1.924
	ActHIB	290	290	100.0	98.7	100.0	289	99.7	98.1	100.0	243	83.8	79.0	87.8	1.778	**1.643**	1.924
	Pentacel	288	288	100.0	98.7	100.0	287	99.7	98.1	100.0	233	80.9	75.9	85.3	1.820	**1.658**	1.997
Anti-Pneumoniae 5	*Hiberix*	416	416	100.0	99.1	100.0	414	99.5	98.3	99.9	389	93.5	90.7	95.7	3.796	**3.486**	4.134
	ActHIB	286	286	100.0	98.7	100.0	285	99.7	98.1	100.0	269	94.1	90.7	96.5	3.714	**3.367**	4.096
	Pentacel	286	286	100.0	98.7	100.0	285	99.7	98.1	100.0	258	90.2	86.2	93.4	3.475	**3.105**	3.889
Anti-Pneumoniae 6A	*Hiberix*	419	419	100.0	99.1	100.0	417	99.5	98.3	99.9	394	94.0	91.3	96.1	3.439	**3.188**	3.709
	ActHIB	288	288	100.0	98.7	100.0	286	99.3	97.5	99.9	274	95.1	92.0	97.3	3.407	**3.104**	3.738
	Pentacel	284	284	100.0	98.7	100.0	282	99.3	97.5	99.9	267	94.0	90.6	96.5	3.398	**3.068**	3.763
Anti-Pneumoniae 6B	*Hiberix*	422	417	98.8	97.3	99.6	386	91.5	88.4	94.0	256	60.7	55.8	65.4	1.069	**0.959**	1.191
	ActHIB	288	281	97.6	95.1	99.0	263	91.3	87.5	94.3	165	57.3	51.4	63.1	1.021	**0.890**	1.170
	Pentacel	285	278	97.5	95.0	99.0	261	91.6	87.7	94.5	140	49.1	43.2	55.1	0.901	**0.783**	1.036
Anti-Pneumoniae 7F	*Hiberix*	424	424	100.0	99.1	100.0	424	100.0	99.1	100.0	417	98.3	96.6	99.3	4.555	**4.238**	4.895
	ActHIB	291	291	100.0	98.7	100.0	291	100.0	98.7	100.0	286	98.3	96.0	99.4	4.167	**3.839**	4.522
	Pentacel	286	286	100.0	98.7	100.0	286	100.0	98.7	100.0	278	97.2	94.6	98.8	3.845	**3.492**	4.234
Anti-Pneumoniae 9V	*Hiberix*	425	424	99.8	98.7	100.0	424	99.8	98.7	100.0	374	88.0	84.5	90.9	2.581	**2.373**	2.807
	ActHIB	291	291	100.0	98.7	100.0	290	99.7	98.1	100.0	252	86.6	82.1	90.3	2.482	**2.251**	2.737
	Pentacel	286	286	100.0	98.7	100.0	282	98.6	96.5	99.6	237	82.9	78.0	87.0	2.230	**1.996**	2.491

Source: adapted from sBLA 125347.231, CSR HIB-097, table 124, p.289
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
Pentacel = *Pentacel* co-administered with *Prevnar13*, *Engerix-B* and *Rotarix*
GMC = geometric mean antibody concentration, calculated for all subjects.
Antibody concentrations below the cut-off of the assays were given an arbitrary value of one half the cut-off for the purpose of calculating the GMC

N = number of subjects with available results; n/% = number/percentage of subjects with antibody concentrations above the specified cut-off; 95% CI; LL, UL = exact 95% confidence interval; lower and upper limits
Non-inferiority criteria: The lower limit of the 97.5% CIs on the GMC ratios (Subset Hiberix Co-Ad over Sub-cohort ActHIB) for each S. pneumoniae serotype (anti-1, anti-3, anti-4, anti-5, anti-6A, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti-19A, anti-19F and anti-23F) is at least 0.5 (clinical limit for non-inferiority).

Clinical Reviewer's Comment: The lower limit of the 97.5% CIs on the GMC ratios (Subset Hiberix Co-Ad over Sub-cohort ActHIB) for each S. pneumoniae serotype (anti-1, anti-3, anti-4, anti-5, anti-6A, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti-19A, anti-19F and anti-23F) was at least 0.8, which was greater than 0.5 (pre-specified limit for non-inferiority).

6.1.11.2 Analyses of Secondary Endpoints

Analyses of the secondary endpoints included antibody responses to concomitantly administered vaccines based on other immune parameters; the results were consistent with the results of the primary analyses.

6.1.11.3 Subpopulation Analyses

Gender was balanced between male and female for each of the three HIB vaccine groups and white was the major ethnic classification at approximately 60% of all subjects, with African American at 9-10% and American Indian or Alaskan Native at 8%, and any Asian at 7%. Immune response parameters were reported by sex and by race as white or other [other included all subjects not classified as white]. Anti-PRP levels at the ≥1.0ug/mL were generally higher for females compared to males and for other compared to white, however the magnitude of these differences in this reviewer's opinion are not likely to be clinically significant. No such differences were reported for anti-PRP antibodies at the ≥0.15ug/mL level. There were no significant differences by race or by sex for anti-D or anti-T sero-response rates or percentage of subjects achieving titers of ≥0.1IU/mL or ≥1.0IU/mL respectively.

6.1.11.4 Dropouts and/or Discontinuations:

Table 16. Study HIB-097: Number of subjects entered, completed and withdrawn at visit 4 with reason for withdrawal (Primary Total Vaccinated Cohort)

	Hiberix	***ActHIB***	***Pentacel***	**Total**
Number of subjects vaccinated	2963	520	520	4003
Number of subjects completed	2625	470	457	3552
Number of subjects withdrawn	338	50	63	451
Reasons for withdrawal :				
Subject died	0	0	0	0
Serious Adverse Event	5	1	0	6
Non-Serious Adverse Event	9	1	2	12
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0	0
Protocol violation	7	2	2	11
Consent withdrawal (not due to an	109	17	21	147
Migrated/moved from study area	29	0	3	32
Lost to follow-up (subjects with incomplete vaccination course)	33	6	9	48
Lost to follow-up (subjects with complete vaccination course)	37	8	6	51
Sponsor study termination	0	0	0	0
Others	109	15	20	144

Source: adapted from sBLA 125347.231, CSR HIB-097, table 27, p. 196.
Hiberix = Pooled *Hiberix* Lot A, Lot B and Lot C co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
ActHIB = *ActHIB* co-administered with *Pediarix*, *Prevnar13* and *Rotarix*
Pentacel = *Pentacel* co-administered with
P*revnar13*, *Engerix-B* and *Rotarix.*
Vaccinated = number of subjects who were
vaccinated in the study.
Completed = number of subjects who completed
last study visit.
Withdrawn = number of subjects who did not come for the last visit.

Clinical Reviewer's Comment: In general there were six times as many subjects in the Hiberix as compared to the ActHIB and Pentacel groups, and taking this into account there was balance between the groups in terms of completion rates, lost to follow up and protocol deviations. Therefore the subject disposition data would not suggest any bias in the study results by any of these parameters.

6.1.12 Safety Analyses

6.1.12.1 Methods

The analysis dataset used to present safety data is the Safety Analysis Set (SAS), which includes all subjects who received the study vaccine and for whom there is safety data available. There were 3,552 subjects in the SAS, and 8

subjects were excluded because they did not receive the study vaccine per protocol. Approximately 95% of subjects in each of the three study groups completed the safety evaluation forms.

All AEs starting within 31 days following administration of each dose of study vaccine/comparator were recorded into the Adverse Event screen in the subject's eCRF, irrespective of intensity or whether or not they were considered vaccination-related.

The standard time period for collecting and recording SAEs and AEs of specific interest began at the first receipt of study vaccine/comparator and ended 180 days following administration of the last dose of study vaccine/comparator of the primary vaccination course and 180 days following administration of the booster dose, for each subject.

6.1.12.2 Overview of Adverse Events

Solicited Local adverse events included pain, redness and swelling at the injection site. For all groups, injection site pain was the most frequently reported local AE. After the first dose, grade 3 pain at the injection site in the Hiberix group was lower (3.9%) than corresponding rates in the ActHIB and the Pentacel groups (9.0% and 8.9%, respectively). Grade 3 injection site redness and swelling (diameter >20mm for each parameter, respectively) ranged from 0.7-1.5% in the Hiberix group, 0.2 to 4.2% in the ActHib group and 1.9%-3.9% in the Pentacel group. In general, for all study groups, the rate of localized AEs decreased with subsequent doses. Compared to Hiberix and ActHib groups, the rates of solicited AEs were relatively higher in the Pentacel group.

Reviewer Comment: Pentacel contains 5 antigens, compared to 1 antigen in Hiberix and ActHib. Therefore, a higher reactogenicity in the group receiving Pentacel is not unusual.

Solicited General adverse events: The most commonly reported solicited general AEs irritability and drowsiness. Irritability and drowsiness occurred in approximately 3-8% of subjects and drowsiness in 2-4% of subjects, depending on the dose administered; the AE rates did not differ substantially between the three groups. Fever categorized as grade 3 (T>39.5°C) occurred at <1% in each group for each dose.

Table 17. Study HIB-097: Percentage of Children With Solicited Local And General Adverse Events Within 4 Days of Primary Series Vaccination[a] (Dose 1, 2, and 3) With HIBERIX[b], PRP-T[b], or DTaP-IPV/Hib[c], Total Vaccinated Cohort[d]

	HIBERIX %			PRP-T %			DTaP-IPV/Hib %		
	Dose			Dose			Dose		
Adverse Events	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Local[e]									
N	2,828	2,668	2,553	498	481	463	492	469	443
Pain	49.4	45.1	42.8	57.2	53.2	48.2	58.1	50.1	48.5
Pain, grade 3[f]	3.9	2.7	1.9	9.0	5.4	3.5	8.9	3.2	2.7
Redness	18.7	25.4	29.4	23.5	32.0	29.6	25.6	30.7	37.0
Redness, >20 mm	0.9	0.7	0.7	2.2	1.0	0.2	2.0	2.1	2.3
Swelling	13.0	15.4	18.7	18.5	21.8	19.7	19.5	23.7	23.7
Swelling, >20 mm	1.5	1.0	0.8	4.2	2.7	0.6	3.9	1.9	2.0
General									
N	2,830	2,669	2,553	499	480	463	492	469	443
Irritability	68.9	70.4	67.1	76.4	71.0	67.2	73.0	66.7	69.3
Irritability, grade 3[g]	4.1	6.4	4.8	8.4	7.7	5.2	6.1	4.5	3.2
Drowsiness	59.9	54.1	49.3	65.7	55.6	49.5	60.6	51.8	49.7
Drowsiness, grade 3[h]	2.4	2.8	2.2	3.8	2.1	1.3	3.9	2.6	2.7
Loss of appetite	28.7	28.3	27.6	33.3	31.5	27.2	33.5	24.3	24.2
Loss of appetite, grade 3[i]	0.7	1.6	1.5	2.0	1.0	0.4	0.6	0.4	0.5
Fever	13.7	19.2	18.7	16.4	18.8	16.2	11.6	10.9	17.8
Fever, grade 3[j]	0.3	0.6	0.7	0.4	0.4	0.9	0.0	0.0	0.5

Source: adapted from sBLA 125347.231, CSR HIB-097, table 176, p.340

N = all subjects for whom safety data were available.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] HIBERIX and US-licensed monovalent Haemophilus b Conjugate Vaccine (PRP-T) (Sanofi Pasteur SA) were administered concomitantly with PEDIARIX (DTap-HBV-IPV) and PCV13 (Wyeth Pharmaceuticals Inc.) with Doses 1, 2 and 3 and ROTARIX with Doses 1 and 2.

[c] US-licensed DTaP-IPV/Hib (Sanofi Pasteur SA) was administered concomitantly with PCV13 (Wyeth Pharmaceuticals Inc.) and ENGERIX-B with Doses 1, 2 and 3 and ROTARIX with Doses 1 and 2. If a birth dose of hepatitis B vaccine was received, ENGERIX-B was given with Doses 1 and 3.

[d] Study 1: NCT01000974.

[e] Local reactions at the injection site for HIBERIX, PRP-T, or DTaP-IPV/Hib.

[f] Grade 3 pain defined as cried when limb was moved/spontaneously painful.

[g] Grade 3 irritability defined as crying that could not be comforted/prevented normal activity.

[h] Grade 3 drowsiness defined as prevented normal daily activity.
[i] Grade 3 loss of appetite defined as did not eat at all.
[j] Fever defined as ≥100.4°F (≥38.0°C) rectally; Grade 3 fever defined as >103.1°F (>39.5°C) rectally.

Unsolicited general adverse events occurred as follows: At least one unsolicited adverse event within the 31-day post-vaccination period after each vaccination, classified by MedDRA Primary System Organ Class and Preferred Term was, reported for 63.4%, 67.3% and 62.3% of subjects in the *Hiberix*, *ActHIB* and *Pentacel* groups, respectively.
The most commonly reported unsolicited adverse event in the *Hiberix* group was upper respiratory tract infection (URTI) (19.2%) followed by cough (10.4%) and otitis media (9.7%). In the *ActHIB* group, the most commonly reported symptom was URTI (19.2%) followed by cough (9.4%) and otitis media (8.7%). The most commonly reported symptoms in the *Pentacel* group was URTI (18.1%) followed by otitis media (10.6%) and cough (9.6%).
A grade 3 unsolicited adverse event was reported for 10.7%, 12.5% and 9.6% of subjects in *Hiberix*, *ActHIB* and *Pentacel* groups, respectively. The most commonly reported grade 3 unsolicited adverse event was otitis media (at least 2.2%) followed by URTI (at least 1.8%) in the *Hiberix* and *ActHIB* groups. In the *Pentacel* group the most commonly reported grade 3 unsolicited adverse event was otitis media (2.1%) followed by pyrexia (1.5%).

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

Non-fatal SAEs were reported for 107 (3.6%) subjects in the *Hiberix* group, 24 (4.6%) subjects in the *ActHIB* group and 21(4.0%) subjects in the *Pentacel* group during the primary epoch of the study. All except 9 events (five in the *Hiberix* group, three in the *ActHIB* group and one in the *Pentacel* group) had recovered/resolved by the end of the primary epoch and an additional three events (two in the *Hiberix* group and one in the *ActHIB* group) were recovered/ resolved with sequelae.

Five of these SAEs reported for four subjects in the *Hiberix* group (Normal sleep myoclonus reported for one subject at 5 and 6 months of age recovered/resolved with sequelae at the end of the primary epoch, Kawasaki's disease reported for one subject at 6 months of age recovered by the end of the primary epoch, seizure for one subject at 2 months of age recovered at the end of the primary epoch, involuntary muscle contraction of leg for one subject at 4 months of age recovered by the end of primary epoch) and one SAE reported for a subject in the *ActHIB* group (possible seizure at 1 month of age recovered by the end of the primary epoch) were considered by the clinical investigator as related to the study vaccination. However, after review by the GSK medical team, the SAE of

Kawasaki's disease and the SAE of involuntary muscle contraction were deemed to not be related to vaccination and therefore mention of these two SAEs were deleted from the label. In this reviewer's opinion, after reviewing all of the available data on the SAEs, the reporting of the SAEs seems appropriate.

6.1.12.5 Adverse Events of Special Interest (AESI)

AEs of specific interest (New onset of chronic diseases (NOCD)) were reported for 3.6% of subjects in the *Hiberix* group, 4.2% of subjects in the *ActHIB* group and 2.9% of subjects in the *Pentacel* group.

The most commonly reported symptom in the *Hiberix* group was dermatitis atopic (0.9%) followed by asthma (0.8%). In the *ActHIB* group, the most commonly reported symptom was asthma (1.2%) followed by eczema (1.0%). The most commonly reported symptoms in the *Pentacel* group were food allergy and asthma (0.8%) followed by eczema (0.6%).

6.1.13 Study Summary and Conclusions

The anti-PRP antibody responses from study HIB-097, as a whole, support use of Hiberix immunization for the indication requested in this sBLA application, which is for the primary series at 2, 4 and 6 months of age. In this reviewer's opinion:

- Lot consistency: although the non-inferiority [NI] criteria for lot consistency were not met primarily because Hiberix Lot B GMCs were higher relative to the GMCs for Lots A and C, however, the GMCs for the 3 Hiberix lots were within the range of GMCs reported for other Hib vaccines; therefore, the statistical significant difference was not clinically relevant. No manufacturing concerns were identified by the CBER CMC reviewer.
- Immunogenicity (inferred effectiveness): Although NI criteria were not met for the difference in percentage of subjects with anti-PRP concentration $\geq$1.0ug/mL (Hiberix group vs. ActHib group), the percentages of subjects with anti-PRP concentration $\geq$0.15ug/mL prior to the booster dose were similar, suggesting that the statistically significant differences are not clinically concerning. Also, the anti-PRP responses following completion of the Hiberix primary vaccination series (2, 4 and 6 months of age) were higher than corresponding responses following the third dose of Pentacel, which is also a US licensed vaccine.

The safety profile of Hiberix is acceptable. The frequencies of AEs following Hiberix vaccination is within the range of AEs rates reported for other pediatric vaccines routinely administered to infants

9.1.1 Human Reproduction and Pregnancy Data

There are no human reproduction data available for Hiberix and a Pregnancy registry is part of the PVP.

9.1.2 Use During Lactation

n/a

9.1.3 Pediatric Use and PREA Considerations

A partial waiver to conduct studies in infants from birth to 6 weeks of age and in children >5 years of age was granted. PREA requirements for age groups 6 weeks to 15 months were fulfilled by safety and immunogenicity data from study HIB-097. Study HIB-097 results were presented to PeRC on 11-18-2015 and the committee agreed that PREA requirements had been met.

9.1.4 Immunocompromised Patients

There is no current data on the use of Hiberix in immunocompromised patients. The proposed label acknowledges this fact and recommends clinical discretion in the use of Hiberix in immune-compromised patients.

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10. Conclusions

Hiberix immunization for the primary vaccine series at 2, 4 and 6 months of age, based upon anti-PRP Ab levels achieved, is likely to protect from invasive *Haemophilus influenzae* type b disease during the interval from age 2 months to the recommended booster dose at age 15 months [15 months to 4 years of age]. The safety data is acceptable and demonstrates local and systemic Adverse Events that are commonly seen in routine pediatric vaccines with no safety signals identified in the single study that supports this efficacy supplement. The applicant's submission for Hiberix as a three dose primary series should be approved and this would allow Hiberix to be used for the full primary vaccination series plus the recommended booster dose at 15 months which was approved in the original BLA in 2009.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *Haemophilus influenzae* type b invasive disease is a significant cause of pediatric morbidity and mortality • Although there are antibiotics available to treat invasive HIB disease, the diseases themselves are often of rapid progress and fulminant nature and there were significant morbidities and mortality attributable to invasive HIB disease in the pre-HIB vaccine era	• *Haemophilus influenzae* type b invasive disease is a serious pediatric infection • Primary prevention of invasive HIB disease is an important public health goal
Unmet Medical Need	• In the U.S. there are currently two licensed HIB vaccines for the full series of primary and booster vaccination and Hiberix has been licensed in the U.S. since 2009 only for the booster dose • There have been periods of time when there were HIB vaccine shortages in the U.S. in the past ten years and such shortages could occur again in the future	• Shortage of HIB vaccines would represent an unmet medical need for HIB vaccine in the U.S.
Clinical Benefit	• More than 25 years of HIB vaccine data support the assertion that invasive HIB disease is significantly reduced when HIB vaccine is routinely administered as a 2, 4, 6 month primary series with a 15 month booster dose. • There is a hypothesis that nasal carriage of HIB is reduced with the use of protein-conjugate HIB vaccines but this hypothesis has not been demonstrated in clinical studies • The clinical benefit of HIB vaccination does not appear to be as great for Native Americans as for other ethnic groups for reasons that are not clear; however there has still been substantial reduction in the rates of invasive HIB disease in this subgroup with the routine use of conjugate HIB vaccines.	• The evidence for clinical benefit of routine HIB vaccination in pediatric patients is compelling. • The benefit of routine HIB vaccine in pediatric patients who are Native American is less compelling but is still quite significant • It is unknown whether the addition of more immunizations to the HIB vaccine schedule or higher doses of antigen would confer increased benefits to Native American patients
Risk	• The most substantial risks of vaccination with Hiberix are associated with the inflammation produced at the injection site. Erythema, swelling, and pain are very common. However, most injection site reactions are mild in severity, and they resolve relatively quickly and without sequelae. • No other safety signals were apparent in pediatric subjects aged 2 to 6 months. • There is a theoretical risk that Hiberix vaccination may be associated with	• All the evidence indicates that the risk of vaccination with Hiberix is minor and is consistent with the risks of other primary pediatric vaccinations. • Routine pharmacovigilance should suffice in identifying the risk of vaccine failure with Hiberix given for the

	greater risk of vaccine failure compared to ActHIB based on immune response criteria, especially between the ages of 7 and 14 months, however the 19 years of post-marketing surveillance of Hiberix outside the U.S. would not support that such a risk exists.	primary series and the booster dose.
Risk Management	• There are no safety signals with Hiberix that would require a specifically tailored risk management strategy • The possible risk of vaccine failure leading to an increased rate of invasive HIB disease in patients who receive Hiberix for the primary series and the booster dose can be managed with the PVP as presented by the applicant	• If Hiberix were approved for pediatric patients aged 2 to 15 months, as the primary series of three vaccinations at 2.4 and 6 months, then routine measures, such as the package insert and the current pharmacovigilance plan, would be adequate to manage the risks

Insert table number and title here

11.2 Risk-Benefit Summary and Assessment

The effectiveness of Hiberix immunization as the primary series of vaccinations at 2,4 and 6 months of age is demonstrated by the immunogenicity data submitted in this supplement. In the context of this sBLA, the safety profile of Hiberix in infants is acceptable and is adequately described in the package insert. The overall risk-benefit is favorable. Continued safety surveillance through routine pharmacovigilance is sufficient. Based upon the risk-benefit assessment, this reviewer recommends approval of this efficacy supplement.

11.3 Discussion of Regulatory Options

Hiberix was previously approved for the booster dose at 14 month to 4 years under accelerated approval. The immune response and safety data presented in this submission support traditional approval of the primary series at 2, 4. and 6 months of age and fulfills the PREA requirement from the 2009 approval of Hiberix. Verification of clinical benefit of the booster dose in the 14 months to 4 year olds is pending submission of Study Hib-097 immunogenicity non-inferiority data in 14 month to 4 year olds. Although Study Hib-097 was designed to evaluate safety and immunogenicity of the primary series and verification of clinical benefit of the booster dose, at the time of the pre-BLA consultation the data pertaining to the booster dose was not complete and, in addition, data that is submitted in support of a change in indication cannot be submitted along with data to fulfill an accelerated approval PMR.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of Hiberix for the primary series, administered at 2, 4 and 6 months of age.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed during this efficacy supplement review cycle and specific comments on the labeling were provided by CBER to the applicant who made the requested revisions. All issues were satisfactorily resolved. The following changes were made to the label; under “Indications and Usage” the label now states “approved for use in children 6 weeks through 4 years of age (prior to fifth birthday).”; under “Warnings and Precautions” a statement concerning apnea in premature infants following IM vaccination has been added; and the immunogenicity and safety data from Study HIB-097 were added to the label.

11.6 Recommendations on Post marketing Actions

No additional post-marketing studies are needed as a result of the clinical review of the safety and immunogenicity data in this s BLA. The submitted PVP, which describes continued routine pharmacovigilance, is adequate,